Chemical Safety for Sustainability
National Research Program
Strategic Research Action Plan, 2019-2022

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List of Acronyms

A-E	Air and Energy
AEP	Aggregate Exposure Pathways
AOPs	Adverse Outcome Pathways
APCRA	Accelerating the Pace of Chemical Risk Assessment
CEC	Chemicals of Emerging Concern
CEH PACT	Children's Environmental Health Partner Alliance Coordination Team
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CompTox	Computational Toxicology
CSA	Chemical Safety Analytics
CSS	Chemical Safety for Sustainability
CWA	Clean Water Act
DMSO	Dimethyl Sulfoxide
DNT	Developmental Neurotoxicity
DOD	Department of Defense
ECHA	European Chemical Agency
ETAM	Ecotoxicological Assessment and Modeling
ECOS	Environmental Council of the States
ECOTOX	Ecotoxicology Knowledgebase
EDSP	Endocrine Disruptor Screening Program
EMT	Emerging Materials and Technology
ENMs	Engineered Nanomaterials
ESA	Endangered Species Act
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act
FY	Fiscal Year
HHRA	Human Health Risk Assessment
HSR/HSRP	Homeland Security Research Program
HTT	High-Throughput Toxicology
HTTK	High-Throughput Toxicokinetics
ISI	Informatics, Synthesis, and Integration
IT	Information Technology
MCCs	Methodologically Challenging Chemicals
NaKnowBase	Nanomaterials Relational Database
NAM	New Approach Methodology
NAS	National Academy of Sciences
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NRP	National Research Program
NSTC	National Science and Technology Council
OCMs	Organotypic Culture Models
OCSPP	Office of Chemical Safety and Pollution Prevention
OLEM	Office of Land and Emergency Management
OPP	Office of Pesticide Programs
OPPT	Office of Pollution Prevention and Toxics

ORD	Office of Research and Development
OSCP	Office of Science Coordination and Policy
OW	Office of Water
RapidTox	RapidTox Dashboard
PCBs	Polychlorinated biphenyls
PFAS	Per- and Polyfluoroalkyl Substances
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctanesulfonic acid
PIP	Pathfinder Innovation Project
PO	Program Office
QSAR	Quantitative Structure Activity Relationship
RARE	Regional Applied Research Effort
RCRA	Resources Conservation and Recovery Act
REMD	Rapid Exposure, Modeling, and Dosimetry
RO	Regional Office
SAP	Science Advisory Panel
SDWA	Safe Drinking Water Act
SeqAPASS	Sequence Alignment to Predict Across Species Susceptibility
SHC	Sustainable and Healthy Communities
SSWR	Safe and Sustainable Water Resources
STAR	Science to Achieve Results
StRAP	Strategic Research Action Plan
Tox21	Toxicology Testing in the 21st Century
ToxCast	Toxicity Forecaster and Biological Materials
TSCA	Toxic Substances Control Act
USEPA	United States Environmental Protection Agency
VTM	Virtual Tissue Modeling

Executive Summary

The Environmental Protection Agency's (EPA) Chemical Safety for Sustainability (CSS) National Research Program (NRP) is transforming chemical risk-based decisions by conducting high-quality, innovative scientific research to support the Agency, states, tribes, and other stakeholders in fulfilling their shared objectives to protect human health and the environment. CSS has a history of conducting innovative science and is a hub of global scientific expertise and leadership in many areas, such as computational toxicology, high-throughput toxicology, rapid exposure science, and complex systems science.

The pressing environmental and health challenge in chemical safety evaluations has been, and continues to be, a lack of sufficient information on most chemicals used in commerce, industry, and agriculture. Traditional approaches for evaluating chemical safety have been unable to keep pace with innovations in chemical design, synthesis, and use. Thus, many chemicals have little data available to make science-based decisions. In addition, chemicals of emerging concern, such as per- and polyfluoroalkyl substances (PFAS), heighten the need for rapid, scientifically-based approaches to evaluate chemical safety.

This CSS Strategic Research Action Plan (StRAP) reflects the priority needs of Agency program and regional offices, states, tribes, and external stakeholders as determined through extensive, systematic consultations and engagements conducted over the last year. The CSS StRAP reflects EPA's Strategic Plan and the Office of Research and Development's Strategic Plan and is firmly rooted in statutory authorities that authorize research to fulfill the Agency's mission. The research and development work outlined in this StRAP is informed by recent scientific advancements in the chemical safety field, many of which were developed by Agency scientists.

CSS research will positively impact and advance chemical safety assessments through several anticipated accomplishments, including:

- A chemical safety informatics infrastructure to support decision makers;
- High throughput hazard and exposure approaches to fulfill data needs;
- Complex systems science to inform interpretive frameworks and exploit the use of new approach methodologies (NAMs);
- Approaches to extrapolate data among chemicals, species, life stages, and biological levels of organization to extend the applicability of existing data; and,
- Consideration of sensitive populations and life stages in chemical safety evaluations.

CSS seeks to lead the development of new approach methodologies and take advantage of scientific and technological developments that advance efficient evaluations of chemical safety. Through a robust intramural research program, collaborations with partners and stakeholders, including academia and other governmental organizations, and support from an innovative extramural grants program, CSS will build a broader understanding of biology, chemical toxicity, and exposure while providing more rapid, cost-effective approaches that protect human health and valued ecological resources and services.

Introduction

Chemicals comprise the key building blocks for most of the products used by and benefiting a prosperous society. The Environmental Protection Agency (EPA), along with other federal partners, states and tribes, plays a central role in evaluating potential impacts of chemicals on human health and the environment. EPA's objectives are to provide efficient, transparent, and scientifically robust approaches to evaluating chemical safety and to continually improve these approaches in response to scientific and technological advancements. To achieve this, EPA applies advanced toxicological and exposure methods, data, tools, models, and information access to make better informed and more timely decisions about the safety of chemicals, many of which have not been thoroughly evaluated for potential risks to human health and the environment. EPA's Chemical Safety for Sustainability (CSS) National Research Program (NRP) is designed to support EPA's priority of reducing risks associated with exposure to chemicals in commerce, consumer products, food, and the environment.

EPA's Office of Research and Development (ORD) developed this *Chemical Safety for Sustainability Strategic Research Action Plan 2019–2022* (CSS StRAP) to articulate the chemical safety research needs of ORD's partners, outline strategic outputs to address those needs, and guide development of research implementation plans. The 2019-2022 CSS StRAP builds upon previous CSS StRAPs (USEPA, 2012; USEPA, 2015) and continues a practice of conducting innovative scientific research and development aimed at solving the problems encountered by Agency partners and stakeholders. The current CSS StRAP evolved through a series of meetings, workshops, and consultations with Agency partners, ORD scientists, and interactions with external stakeholders. It lays out a vision of research and development that is focused on both near- and long-term needs and delivering scientific products that inform implementation of environmental regulations and Agency rulemaking and decisions.

ORD refers to EPA Program and Regional Offices, states, and tribes (including organizations and subsidiaries thereof) as partners.

ORD considers industry, professional groups, and non-governmental organizations that have interests in chemical safety and management as stakeholders.

The CSS StRAP is one of six research plans, one for each of EPA's national research programs in ORD[1]. The six research programs are:

- Air and Energy (A-E);
- Chemical Safety for Sustainability (CSS);
- Homeland Security Research Program (HSRP);
- Human Health Risk Assessment (HHRA);
- Safe and Sustainable Water Resources (SSWR); and,
- Sustainable and Healthy Communities (SHC).

Research to Support EPA and ORD Strategic Plans

EPA's Strategic Plan for FY2018-2022 (USEPA, 2018a) outlines the need for chemical safety research. Under Objective 1.4, ***Ensure Safety of Chemicals in the Marketplace***, the Agency defines ambitious goals to implement the Toxic Substances Control Act (TSCA), and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), *"…to ensure new and existing chemicals and pesticides are reviewed for their potential risks to human health and the environment and actions are taken when necessary."* Further,

[1] https://www.epa.gov/research

under Objective 3.3, **Prioritize Robust Science**, the Agency "*will identify, assess, conduct, and apply the best available science to address current and future environmental hazards, develop new approaches, and improve the scientific foundation for environmental protection decisions*."

> ***The Agency will produce innovative tools that accelerate the pace of data-driven evaluations, enable knowledge-based decisions that protect human health, and advance the science required to anticipate and solve problems.***
> *FY 2018-2022 EPA Strategic Plan*

ORD's Strategic Plan (USEPA, 2018b) responds to and builds upon the Agency's Strategic Plan. StRAPs for ORD's six research programs outline specific research activities that address objectives in both strategic plans and the needs of our state and tribal partners. Active partnerships can and do occur with our partners and are reflective of the focus on ORD conducting solutions-driven research.

CSS research will provide the scientific foundation required for risk assessments that help inform decisions about the use of chemicals and protect human health and the environment. CSS research will also enable the Agency to evaluate and predict impacts from chemical use and disposal and will provide the Agency, states, and tribes with information, tools, and methods to make better informed and more timely decisions about the thousands of chemicals used in commerce, industry, and agriculture.

Statutory and Policy Context

Managing chemical risks to protect human health and the environment, including the conduct of supporting scientific research, is authorized and/or mandated in several statutes. The CSS research portfolio is largely focused on requirements authorized under TSCA, FIFRA, the Food Quality Protection Act (FQPA), Federal Food, Drug, and Cosmetic Act (FFDCA), the Safe Drinking Water Act (SDWA), Resource Conservation and Recovery Act (RCRA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), and Endangered Species Act (ESA). Chemical assessment, regulation, and management associated with these statutes are implemented by EPA's program offices, including the Office of Chemical Safety and Pollution Prevention (OCSPP), Office of Land and Emergency Management (OLEM), and Office of Water (OW). CSS works closely with each of these offices to ensure that research is designed to support current and future needs. Furthermore, due to the fundamental nature of CSS's work, CSS data, tools, and models are often used to inform decisions made under other authorities, both federal and state.

Partner and Stakeholder Engagement

Defining the problems and needs of partners and stakeholders is a necessary step to designing a research agenda that is both responsive and actionable. To create this StRAP, CSS has been engaging partners and stakeholders since mid-2017 to assess their problems and needs. The highest priority needs are presented in Appendix 1. CSS used several approaches to foster dialog, including: conducting topical workshops, briefing partners on CSS StRAP development, conducting regularly scheduled consultations, collaborating with partners on programmatic strategies and plans, participating in state and tribal discussions, and providing opportunities for partners to review the CSS StRAP at different stages of development (Appendix 2).

Most of the needs identified by Agency partners were focused on toxicological considerations, such as hazard and exposure, to support chemical risk assessment and risk management decisions. General themes were to provide better information, more quickly, with some emphasis on the development and adoption of new approach methodologies to accomplish those objectives. The research needs

presented in Appendix 1 are generally expressed in the context of specific programmatic needs, with the research needs of TSCA, FIFRA and FQPA driving much of the CSS research portfolio. For example, OCSPP-OPPT expressed several needs specific to supporting implementation TSCA. These research needs included:

- Research towards the development of alternative, non-vertebrate chemical safety tests and methods (TSCA, Section 4);
- Improved approaches and guidance for the evaluation of new chemicals (TSCA, Section 5); and,
- The development of rapid, reliable, and economical screening techniques and scientific procedures supporting the review, prioritization, and risk evaluation of existing chemicals (TSCA, Section 6).

OCSPP-OPP has similar scientific needs to OPPT, albeit in a different programmatic context and with different timelines. These include supporting regular pesticide registration processes, as well as re-registration activities to be completed in 2022 as required under FIFRA. OCSPP-OSCP has more specific needs associated with the EDSP. These focus on completing certain estrogen- and androgen-related aspects of the program in the near term while refining the expectations and needs for understanding effects of chemicals on steroidogenesis and thyroid hormone pathways in the medium and long terms, respectively.

Another driver for CSS research is increased interest in understanding the potential role of environmental chemicals on susceptible populations, such as children and the elderly. This requires research to identify and quantify exposures at relevant life stages, to understand metabolic pathways that are particularly important to susceptible populations, and to investigate the factors associated with differential sensitivity, especially toxicokinetics and toxicodynamics. This type of information will inform public health policy decisions as required under enacted federal environmental statutes such as Executive Order 13045, FQPA, SDWA, and most recently, amended TSCA.

While the specific needs of Agency programs and regions are the primary drivers for ORD research, there is renewed emphasis on addressing the needs of states and tribes. States and tribes are important partners that work cooperatively with EPA and other federal partners, often with delegated authorities to protect human health and the environment. CSS has further developed this relationship by including states and tribes in consultations to identify their most important environmental problems. For example, through these interactions, CSS has developed an increased awareness of the needs to address contaminants of emerging concern, such as per- and polyfluoroalkyl substances (PFAS), and for improved access to integrated chemical safety information on exposure, toxicity, and persistence. A summary of state needs reflected in ORD's research planning activities is presented in Appendix 3.

Evaluating chemical safety is challenging and depends on having available robust science for a wide variety of disciplinary areas and chemical management contexts. Through extensive interactions with Agency, state, tribal, and external stakeholders, common themes emerge that reflect the current problems and needs faced by decision makers. The common themes include:

- The number of chemicals that need to be evaluated is large and is continually changing;
- The timelines and expectations for rapid assessments are often difficult to meet;
- The complexities associated with interpretation of information are often overwhelming;
- Efficient and selective use of relevant information from vast and often disparate data repositories is difficult;

- There are continuing needs for generalizations, interpretive frameworks, and predictive models to take advantage of modern data streams;
- Requirements are high for new high-throughput and alternative test procedures to be considered suitable substitutes for traditional toxicity-testing methods;
- Approaches to extrapolation across chemical space, taxonomic groupings, organismal life stage, and biological levels of organization are needed to inform data-poor situations;
- There are increasing expectations to address sensitive populations and life stages; and,
- There is legislative direction and societal pressure to reduce, refine, and replace the use of vertebrate animal testing.

These common themes are reflected throughout the CSS StRAP and are reflected in the development of CSS Research Areas and the identified strategic outputs.

Environmental Problems and Program Objectives

Continuing innovation in chemical design, production, and use in commerce, industry, and agriculture is a key feature of a vibrant American economy. In addition to the inventories of existing chemicals, new chemicals and new chemical uses are continually introduced to the marketplace to improve a wide variety of products and processes. Because certain chemicals may have adverse impacts to humans and ecological species, chemical manufacture, use, and disposition need to be managed to minimize potential effects to human health and the environment. Efficient and effective management of chemical safety is a demanding Agency priority. For example, the TSCA active inventory alone contains over 40,000 chemicals and hundreds more are introduced every year. However, the information for the majority of the 40,000 chemicals is incomplete to fully evaluate potential risks to human health and the environment, especially for potentially vulnerable and sensitive populations, such as children. Traditional toxicity testing methods for evaluating risks from exposures to individual chemicals are expensive, time consuming, and provide an incomplete understanding of chemical interactions with biological systems. To address this critical challenge, rapid, efficient, and cost-effective approaches are needed to prioritize, screen, and evaluate chemicals for safety using scientifically-sound and transparent processes.

The National Academies of Science (NAS) recognized the need to modernize the field of toxicology through three seminal reports on toxicity testing, exposure science, and risk evaluation. The first report, *Toxicity Testing in the 21st Century: A Vision and a Strategy* (NAS, 2007), provided support for a paradigm shift in toxicology that favored the development and application of *in vitro* systems and computational modeling to replace expensive and time-consuming *in vivo* testing approaches. This report supported the concept of conducting high-throughput toxicity testing for thousands of chemicals with *in vitro* assays through efforts such as the interagency Tox21 Program (Thomas et al. 2018) and EPA's ToxCast (Kavlock et al. 2012; Richard et al. 2016). Both efforts are foundational to developing computational toxicology approaches. The second NAS report that guided the development of the CSS Program, *Science and Decisions: Advancing Risk Assessment* (NAS, 2009), provided practical recommendations to address the challenges of risk assessment, including data gaps, uncertainties, and assessment complexities. The recommendations focused on improving and accelerating risk-based decision making and are applicable to nearly all of EPA's environmental legislation. The third report, *Exposure Science in the 21st Century: A Vision and a Strategy* (NAS, 2012), supported complementary shifts for the exposure sciences, introducing a vision for computational exposure science parallel to the computational toxicity approaches introduced in the 2007 NAS report. The third report also supported expanding exposure

beyond the traditional external view to include the internal exposure, which provides the critical linkage between external exposure and effects.

In addition, other NAS reports inform components of the program, including work on engineered nanomaterials (NAS, 2012b), design and use of safer chemical alternatives (NAS, 2014), evaluation of pesticide impacts on threatened and endangered species (NAS, 2013), endocrine disruption chemicals (NAS, 2014b), and the use of new science in risk assessment (NAS, 2017).

EPA's needs in assessing chemical safety are broad and varied according to the legislative authorities, rules, and policies associated with different statutes. In response, CSS develops both fundamental research products that can be applied to common needs among multiple Agency partners and stakeholders; and, targeted research products and outputs to meet specific programmatic and partner needs.

Problem Statement

Tens of thousands of chemicals are currently in use and hundreds more are introduced to the market every year. Currently available information provides an incomplete understanding of the potential risks of chemicals to human health and the environment, which results in EPA programs and regions, states, tribes, and others making many risk-based decisions with limited hazard and exposure data. Additionally, traditional approaches to evaluate chemical toxicity and exposure are expensive and do not fully reflect all biological responses and exposure pathways. Improved measurement and modeling approaches are needed to evaluate chemical toxicity and exposure, based on strong science and that are rapid, cost-effective, and accepted by regulatory and industry communities, non-governmental organizations, and the public.

Program Vision

CSS will develop the data, information, tools, and models that will enable our partners and stakeholders to make informed and timely decisions concerning the potential impacts of environmental chemicals on human health and the environment. CSS science will be transformative, leading to improved science-based approaches that build broader understanding of biology, chemical toxicity, and exposure while providing more rapid, cost-effective approaches that protect human health and valued ecological resources and services.

Program Objectives

CSS conducts high-quality chemical safety research and development to provide the fundamental data, knowledge infrastructure, and complex systems understanding required to develop tools for rapid chemical evaluation and to predict potential impacts from chemical use. CSS translates research results to provide solutions and technical support to EPA partners and stakeholders.

CSS research is guided by the following four objectives:

- **Objective 1: Build Knowledge Infrastructure.** CSS will use advanced information technology tools to mine ever-expanding data sources for relevant information on chemical properties, structure, toxicity, and exposure. CSS will focus efforts to annotate, curate, and efficiently serve chemical information in formats usable to stakeholders and will generate high-quality, peer-reviewed data to fill high-priority gaps in existing knowledge. CSS will address this objective by integrating data across research activities. CSS is moving towards becoming a “first-stop-shop”

for chemical information needed by EPA partners, stakeholders, and the public and will incorporate user feedback in designing the supporting information systems and user interfaces.

- **Objective 2: Develop Tools and Models for Chemical Evaluation.** In addition to developing a chemical information infrastructure, CSS must also provide additional content and information to better inform specific decisions. CSS will continue to develop and apply rapid, efficient, and effective tools and models for chemical safety evaluations. CSS will also combine different types of data in new ways to characterize impacts of chemicals to human health and the environment.

- **Objective 3: Promote Complex Systems Understanding.** CSS research activities will investigate the emergent properties in complex chemical-biological systems by probing how disturbances and changes in one part affect the entire system. By forming a detailed understanding of systems behavior, CSS research will expand predictive capabilities that can anticipate and inform future chemical safety challenges, including chemical and biological extrapolation, as well as extrapolation across biological levels of organization.

- **Objective 4: Translate and Actively Deliver.** Solutions-driven research is emphasized throughout the CSS research portfolio. CSS will focus on the delivery, demonstration, and application of CSS data, tools, and models through case-studies and partner engagement to inform immediate, high-priority needs. By engaging early and often, and with continued engagement after delivery of science products, CSS will promote the mutual understanding of needs and solutions, thereby enhancing the impact of CSS research products.

Research Topics and Research Areas

CSS is organized around three broad research topics that include similar areas of disciplinary expertise and capability relevant to the partner needs. Within each research topic are research areas that focus expertise and capabilities on deliverable products of specific research and development activities (Table 1). This section presents a description of each topic and research area and lists the strategic outputs (Appendix 1) that will guide research implementation by ORD. Each strategic output is led by a research area team during implementation. By design, CSS research is integrated across research areas. Therefore, each of the 48 strategic outputs in CSS may be supported by research efforts from one or more research areas.

Table 1: CSS Research Topics and Research Areas

Topic	Research Areas
Chemical Evaluation	High-Throughput Toxicology (HTT)
	Rapid Exposure Modeling and Dosimetry (REMD)
	Emerging Materials and Technologies (EMT)
Complex Systems Science	Adverse Outcome Pathways (AOP)
	Virtual Tissue Modeling (VTM)
	Ecotoxicological Assessment and Modeling (ETAM)
Solutions-Driven Translation and Knowledge Delivery	Chemical Safety Analytics (CSA)
	Informatics, Synthesis, and Integration (ISI)

Topic 1: Chemical Evaluation

Research under the Chemical Evaluation topic will provide rapid methods and high-throughput data for risk-based evaluations of new and existing chemicals and emerging materials. This topic will emphasize development and application of new approach methodologies to rapidly generate exposure and hazard information for chemicals and emerging materials and technologies. The High-Throughput Toxicology (HTT) Research Area focuses on hazard profiling of chemicals using rapid toxicity testing approaches. The Rapid Exposure Modeling and Dosimetry (REMD) Research Area focuses on modeling and forecasting chemical exposures across various scenarios relevant to human and ecological exposure assessments. The third research area, Emerging Materials and Technologies (EMT), addresses hazard and exposure data needs of engineered products that are often not amenable to the types of approaches used to characterize conventional chemicals. The current focus of EMT is on engineered nanomaterials.

Research Area: High-Throughput Toxicology

For most chemicals, the availability of data and information to assess the potential toxicity to humans and other species is limited or incomplete. Existing chemical inventories and the introduction of new chemicals have driven the need for rapid assessment approaches. The High-Throughput Toxicology (HTT) Research Area is focused on addressing the limitations of current chemical testing methods and fulfilling EPA's need to evaluate large numbers of chemicals for potential adverse human and ecological effects. The HTT Research Area will design, develop, and apply new approach methodologies (NAMs) for testing chemicals. These high-throughput approaches will rapidly generate chemical hazard data on specific endpoints of interest to partners and stakeholders. These new approaches will help prioritize, screen, and evaluate chemical safety for thousands of compounds and reduce reliance on traditional toxicity tests.

Building on the successes of previous research efforts to implement HTT approaches (e.g., ToxCast[2], EDSP21, and Tox21[3]), the focus of these strategic outputs will be methods development and data generation for priority pathways of toxicological relevance and for under-represented chemical classes that are not amenable to current HTT testing methods (see Appendix 1 for complete table of strategic outputs). Scientific and technological advances have paved the way for using additional NAMs in the HTT research area. These represent opportunities for HTT to adapt and evolve new high-throughput approaches to meet the Agency's chemical safety mission.

Research products from the HTT Research Area will enable EPA partners and stakeholders to make better, more timely decisions about chemicals by increasing toxicological information for more biological endpoints and for more chemicals while reducing the use of vertebrates for testing.

Strategic Outputs:

- Develop assays, models, data, tools, and interpretive frameworks to support more rapid and cost-effective approaches to screen large inventories of chemicals for their abilities to impact estrogen, androgen, thyroid, and steroidogenesis pathways. (Strategic Output HTT-1)
- Develop, evaluate, apply, and interpret a battery of assays for developmental neurotoxicity (DNT) to reduce uncertainties in chemical safety evaluations. (Strategic Output HTT-2)

[2] https://www.epa.gov/comptox/toxcast
[3] https://tox21.gov

- Develop and apply medium- to high-throughput methods to test and deliver novel hazard data on methodologically challenging chemical classes, such as volatile and non-dimethylsulfoxide (DMSO)-soluble chemicals. (Strategic Output HTT-3)
- Develop and apply methods and approaches to advance a tiered, high-throughput toxicity testing strategy including high-throughput and high-content methods (e.g., transcriptomics, phenotypic profiling, and other methods) that address key information needs of assessments. (Strategic Output HTT-4)

In vitro assay limitations introduce uncertainty when using high-throughput data to inform chemical safety decisions. For example, lack of endogenous metabolism/bioactivation in existing high-throughput approaches could result in hazard mischaracterization for chemicals that undergo biotransformation. Thus, there is an urgent need to develop approaches to address sensitivity and specificity concerns resulting from the limitations of *in vitro* assays.

Strategic Outputs:

- Develop methods to incorporate endogenous and exogenous xenobiotic metabolism activity in *in vitro* assay systems. (Strategic Output HTT-5)
- Evaluate and develop predictive models of the disposition of chemicals in *in vitro* test systems. (Strategic Output HTT-6)

In addition to accelerating risk-based evaluations of existing chemicals, HTT research has potential applications for emerging materials and immediate environmental issues, such as contaminants of emerging concern (CECs) in the environment. Examining the utility of high-throughput approaches for CECs requires collaboration with EPA partners and stakeholders in developing fit-for-purpose case studies.

Strategic Outputs:

- Develop a PFAS screening library and deliver information from integrated exposure and effects studies. (Strategic Output HTT-7)

The majority of existing HTT methods are based on human or other mammalian species, which results in an underrepresentation of pathways that are relevant to some ecological species. Although advanced extrapolation techniques can be used to infer activities across species where the toxicological target is taxonomically conserved, determining potential ecological impacts of chemical exposure requires alternative species approaches for high-throughput toxicity testing.

Strategic Output:

- Develop, evaluate, and apply non-mammalian high-throughput toxicity tests for priority endpoints and pathways in ecological species. (Strategic Output HTT-8)

Research Area: Rapid Exposure Modeling and Dosimetry

The Rapid Exposure Modeling and Dosimetry (REMD) Research Area addresses multiple EPA program office needs for exposure and dosimetry information. REMD will develop data, tools, models, and approaches to rapidly generate scientifically defensible exposure and dosimetry estimates for new and existing chemicals found in consumer products and the environment. This research will also include development of advanced chemical monitoring approaches, refinement of exposure pathways and factors, and high-throughput toxicokinetics to support dosimetry estimates associated with HTT hazard

data. In concert with the toxicity information generated in the HTT Research Area, estimates of human and ecological exposures developed in REMD represent critical inputs for high-throughput, risk-based prioritization and screening of chemicals.

Experimental measurements and predictive modeling are essential components in exposure assessment. While collection of measured data is important to refine and improve chemical exposure models, it is particularly important to have confidence in exposure models when they are the only means of estimating exposures for pathways with limited source emissions data and data-poor parameters. Currently, the collection of monitoring data and other model inputs lag behind the data needs for model development. As a result, the focus of several REMD strategic outputs is to address the gaps in data collection and the curation of model inputs.

Products from the REMD Research Area will provide chemical exposure information supporting risk assessments conducted by EPA partners and stakeholders for both new and existing chemicals.

Strategic Outputs:

- Collect and curate exposure factor-related data (behavior patterns, habits and practices, product composition, chemical fate and transport) for use as inputs to models used in higher tier assessments. (Strategic Output REMD-1)
- Develop experimental methods, data, and consensus exposure models for various exposure pathways (e.g., consumer, occupational, ambient, indoor environment, and ecological scenarios) that enable high-throughput exposure predictions for chemicals. (Strategic Output REMD-2)
- Develop end-of-use models for tracking chemicals in waste streams and the subsequent environmental releases and worker exposures, including novel end-of-life scenarios based on chemical type and function. (Strategic Output REMD-3)
- Expand capabilities of generic scenario processes by minimizing development time and increasing the number of available scenarios. This includes developing models and tools for estimating common scenario needs, data, and methods for estimating new chemical applications, life cycle releases, and occupational exposure support. (Strategic Output REMD-4)
- Develop methods, approaches, and frameworks to enable rapid exposure evaluations for PFAS chemicals. (Strategic Output REMD-5)

Uncertainties in relating *in vitro* assay doses to human environmental exposure concentrations limit application of high-throughput data to chemical safety decisions. To address these uncertainties, rapid toxicokinetic approaches are needed to convert the estimates of route-specific doses generated by the exposure models to the corresponding measures of internal dose (i.e., concentrations at tissue and organismal levels).

Strategic Output:

- Further develop high-throughput toxicokinetic (HTTK) tools to support *in vitro* to *in vivo* extrapolation. Tools to be developed include those needed to address current sources of uncertainty, challenging chemistries, new exposure routes (e.g., inhalation), and the unique exposures received by sensitive subpopulations. (Strategic Output REMD-6)

Estimating chemical exposures requires accurate identification of chemicals occurring in the environment. Current methods and tools characterize only a fraction of chemicals in the environment and struggle to characterize certain materials. The REMD research area is developing models and tools to address data needs for the composition and exposure potential of environmental media, including consumer products.

Strategic Outputs:

- Analyze and evaluate new approaches for generating environmental monitoring data, including non-targeted analysis, to identify critical sources and pathways of human and environmental exposures. Develop best practices, workflows, and cross-laboratory evaluations for next-generation monitoring methods. (Strategic Output REMD-7)
- Develop methods to characterize composition of and exposure to chemical substances of unknown or variable composition, complex reaction products, and biological materials. (Strategic Output REMD-8)

Research Area: Emerging Materials and Technology

Innovations in chemical and material design are rapidly changing the landscape of industrial and consumer products, including novel materials, such as engineered nanomaterials (ENMs), which are incorporated into products to enhance their performance. Emerging materials and technologies often have unique physicochemical properties, warranting specialized approaches for evaluating hazard and exposure. The Emerging Materials and Technologies Research Area will develop, collate, mine, and apply information on ENMs and potentially other emerging materials and technologies, such as biotechnology products, to support risk-based decisions.

Understanding the final disposition of ENMs is important to assess their application-specific safety, made more challenging since the release of and exposure to ENMs through product use, aging, degradation, decomposition, and recycling can be uncertain. For instance, previous research has shown that ENMs released from consumer products are often altered from the ENMs used in the manufacturing of those consumer products. Principles underlying releases and exposure to humans and ecological species varies according to ENM type, product type, product use, environmental conditions, and receiving media type. The following strategic output will evaluate exposure situations that capture a range of priority scenarios, nanomaterials, and product types.

The EMT Research Area will deliver products that inform Agency decisions related to chemicals and chemical materials manufactured using new technologies or packaged in novel forms. This research area currently informs risk-based decisions for nanomaterials.

Strategic Output:

- Evaluate environmental release of ENMs and assess and model human and ecological exposures to ENMs, including data for nano-enabled consumer products (Strategic Output EMT-1)

To provide a centralized resource for Agency partners and stakeholders, ORD developed NaKnowBase (Boyes et al., 2017), a database that captures information originating in Agency research on ENMs. The database was designed to be consistent with the fields and format of external databases yet needs to be integrated within the broader CSS research portfolio to maximize utility.

Strategic Output:

- Develop a user interface for ORD's existing nanomaterials database - NaKnowBase. (Strategic Output EMT-2)

Topic 2: Complex Systems Science

Research conducted in the Complex Systems Science topic is building the scientific foundation to predict adverse outcomes resulting from chemical exposures in various biological contexts. This topic will develop interpretive frameworks and models to put complex information into biological, chemical, and toxicological context. The Adverse Outcome Pathways (AOP) research area focuses on delineating perturbations of specific biological pathways and applying that knowledge to predict apical outcomes based on mechanistic effects. The Virtual Tissue Modeling (VTM) Research Area is bridging the gap between molecular/cellular endpoints and apical outcomes by developing tissue-on-a-chip and *in silico* models, with an emphasis on human developmental endpoints. The Ecotoxicological Assessment and Modeling (ETAM) Research Area will develop integrated approaches to model ecological outcomes across broad taxonomic and ecological scales.

Research Area: Adverse Outcome Pathways

Employing data from new approach methodologies in decision making, such as those being generated by the HTT and REMD Research Areas, requires understanding the role of endpoint measurements in the perturbation of one or more biological pathways. The Adverse Outcome Pathway (AOP) framework provides a systematic and modular structure for organizing and communicating existing knowledge concerning the linkage between chemical exposure (molecular initiating event), intermediate key events along a toxicity pathway, and apical adverse outcomes considered relevant to risk assessment or regulatory decision making. AOPs provide a scientifically-defensible foundation for extrapolating from mechanistic data to predicted apical outcomes. AOP networks can be assembled by evaluating shared nodes or key events in individual AOPs, thereby providing insight into the complex interactions among biological pathways. Whether through individual pathways or pathway networks, the interactions of multiple chemicals present in both simple and complex mixtures will be assessed to facilitate analyses of more realistic environmental exposure scenarios. The AOP Research Area will continue to develop AOPs for high-priority pathways and will emphasize the application of well-developed and curated AOPs to address stakeholder needs through case-study examples.

Products from the AOP Research Area will provide partners and stakeholders with a common, integrating framework with which to link chemical hazard and exposure information from new approach methodologies and better understand linkages between molecular initiating events and apical endpoints.

Successful AOP development is based on having sufficient fundamental knowledge about biological pathways to define and link the results of a perturbation to an adverse effect. Information generated from the HTT, REMD and VTM Research Areas will contribute to this knowledge base to inform AOP development. The outputs under this research area collectively address the need for developing priority pathways, quantitative AOPs for well understood pathways, and novel pathways relevant to underrepresented biological space.

Strategic Outputs:

- Develop AOPs for high-priority pathways, design relevant case studies, and disseminate the results through an AOP knowledgebase. (Strategic Output AOP-1)

- Develop and conduct strategic *in vitro* and *in vivo* studies for high-priority AOPs to help establish validity of NAMs approaches, support predictive model development, and reduce vertebrate animal testing through *in vivo* testing refinements for decision-relevant endpoints. (Strategic Output AOP-2)
- Conduct basic and applied research to understand and define biological points of departure, actionable effect levels, and critical susceptibility factors that need to be considered for application of AOPs. (Strategic Output AOP-3)

AOPs are intended to serve the needs of decision makers, in addition to identifying data gaps that can be addressed to reduce uncertainty in chemical safety evaluations. Case studies provide critical opportunities to facilitate the application of AOPs by decision makers, at the same time informing science needs to support AOPs. The outputs below represent specific applications of AOPs in the context of partner issues.

Strategic Outputs:

- Develop rationale and case studies that apply AOPs and HTT data to inform test-order decisions and establish scientific support for waiving testing requirements for pesticides as part of the implementation of FIFRA. (Strategic Output AOP-4)
- Provide AOP knowledge to support the use of high-throughput data in expedited chemical assessments for data-poor chemicals. (Strategic Output AOP-5)
- Application of data, models, and tools to support development of revised approach to water quality criteria derivations. (Strategic Output AOP-6)
- Conduct site-specific case studies that demonstrate how pathway-based data from existing sources or from effects-based monitoring and surveillance approaches can be used, along with AOPs, to inform risks and associated management actions. (Strategic Output AOP-7)
- Develop AOPs relevant to PFAS chemicals and evaluate applicability across species, chemical groupings, and mixtures. (Strategic Output AOP-8)

Research Area: Virtual Tissue Modeling

To bridge the gap from molecular changes to endpoints relevant for hazard assessment, models of biological systems are needed that can be experimentally probed and computationally simulated. Virtual tissue models connect *in vitro* and *in vivo* observations with complex tissue and organ-level changes. The Virtual Tissue Modeling (VTM) Research Area will focus on developing organotypic culture models and computational agent-based models to test hypotheses regarding organ-specific toxicity of priority chemicals, including pathways and endpoints relevant to human developmental toxicity. For instance, EPA is mandated under the Food Quality Protection Act to screen chemicals for effects on the endocrine system.

The VTM Research Area will provide physical models and mathematical simulations of specific organ systems and developmental outcomes informing risk-based assessments of new and existing chemicals. This research area expands understanding of chemical effects on developmental and reproductive toxicology.

Agency partners and stakeholders support a tiered-testing strategy for characterizing hazards associated with chemical exposures. In tiered approaches, high-throughput data identify chemicals of potential concern. Increasingly more specific secondary assays are then used to link molecular/cellular effects with an apical outcome. To support tiered toxicity-testing approaches, the VTM research area will

develop data and methods to link high-throughput mechanistic toxicity data with apical outcomes at the organ or tissue level.

Strategic Output:

- Develop, characterize, and confirm targeted, mechanistic assays and complex tissue models that bridge between *in vitro* and organismal assays for decision-relevant endpoints. (Strategic Output VTM-1)

Chemical exposures on the developing embryo are important to understand, yet there are limited developmental toxicity data available for most chemicals. Predicting developmental toxicants depends on understanding how developmental processes are impacted by chemical exposure. To address the data gap, VTM research will focus on increasing levels of biological complexity to capture morphological, functional, and behavioral impacts of chemical exposures to the developing embryo.

Strategic Outputs:

- Evaluate the effects of chemical exposure during development on phenotypic responses in human-based *in vitro* and virtual tissue model systems to predict chemical hazard. (Strategic Output VTM-2)
- Develop and apply *in silico* virtual tissue models, agent-based models, and organotypic cell culture models to evaluate and model the effects of chemicals on reproductive and developmental endpoints. (Strategic Output VTM-3)

Research Area: Ecotoxicological Assessment and Modeling

A tiered risk assessment approach is typically used to evaluate and regulate the potential impacts of pesticides and other chemicals on ecological resources. Chemicals are first screened using rapid assessment tools that require minimal data, followed by more detailed and complex assessments for selected chemicals and scenarios. For most chemicals and ecological species, assessments must rely on modeled estimates of exposure and effects. The Ecotoxicological Assessment and Modeling (ETAM) research area will advance efficient and integrated modeling approaches to improve risk assessments of chemicals with limited data, as well as more complex, refined approaches that can address data-rich applications. The integrated models span the sequence of events typical of ecological toxicity, including environmental release, fate and transport, exposure, internal dosimetry, metabolism, and toxicological responses relevant to organismal- and population-level effects in species of interest to Agency decisions.

Products from the ETAM Research Area inform understanding of chemical impacts on ecological species and includes both ecotoxicological and exposure related measurement and modeling activities to inform cumulative risk assessment.

Determining effects of chemicals on ecological species relies heavily on predictive models at scales that are not readily testable, for species that cannot be tested directly, and for spatio-temporally complex chemical exposure scenarios. Integrated environmental fate and transport, exposure, and ecotoxicity models and tools will be developed and demonstrated through case-study applications, including probabilistic models for species and chemicals of interest.

Strategic Outputs:

- Translate and incorporate integrated ecological data and models into Agency risk assessments workflows, including information on uptake, bioavailability, dietary assimilation, biotransformation, bioenergetics, behavior, and population effects. (Strategic Output ETAM-1)
- Develop and apply models to translate data from submitted studies into input for models that estimate population- and landscape-level impacts of pesticide use. (Strategic Output ETAM-2)
- Develop methods and data to assess the impacts of pesticides on honey bee (*Apis mellifera*) and non-*Apis* bees, apply species extrapolation techniques to determine sensitivity differences across species, and further develop and apply honeybee colony simulation models to support pesticide assessments. (Strategic Output ETAM-3)

The ECOTOX Knowledgebase[4] is a curated, interactive database of ecotoxicological information developed by ORD. Outputs from the ECOTOX Knowledgebase are foundational for the majority of Agency ecological assessment and are widely used by partners and stakeholders.

Strategic Output:

- Improve efficiency, enhance analytical capabilities, and periodically update content of the ECOTOX Knowledgebase, in general and for specific chemicals of interest. (Strategic Output ETAM-4)

Extrapolation across species is often a challenge in ecological assessments due to limited availability of ecological toxicity data across broad taxonomic spaces of interest. The CSS outputs will include extrapolation models for species sensitivity, use of surrogate species to fulfill data needs for untestable species, differences in endpoint responses across taxa, and differential metabolic capabilities and capacities between species.

Strategic Outputs:

- Advance approaches for using surrogate species in ecological risk assessment, including uncertainty of cross-species extrapolations in minimal data scenarios. (Strategic Output ETAM-5)
- Develop species-response comparison data with selected high-priority pesticides, linking metabolomics and proteomics with potential molecular initiating events. (Strategic Output ETAM-6)
- Assess similarities and differences in mammalian and fish metabolism pathways for selected groups of chemicals and demonstrate use of mammalian metabolism pathway information to predict biotransformation products in fish. (Strategic Output ETAM-7)

Ecological toxicity assessments are necessary to evaluate the potential hazards of contaminants in the environment. The outputs fill critical needs to conduct these assessments, which employ a broad range of species and endpoints, including molecular biomarkers of exposure and effects, and will be evaluated with field samples collected from impacted sites. Integrated exposure and effects models will be developed for listed species and chemicals with demonstrated co-occurrence.

[4] https://cfpub.epa.gov/ecotox/

Strategic Output:

- Develop improved approaches to protect threatened and endangered species from cumulative exposures to pesticides released to the environment. (Strategic Output ETAM-8)

The effects of high- priority chemicals, including PFAS, on biomarkers, toxicological effects, and ecological impacts will be measured or predicted. Taxa-specific metabolic pathways for different PFAS classes will be evaluated, including experimentation on PFAS compounds that lack comparative metabolism data.

Strategic Output:

- Improve understanding of PFAS bioavailability, bioaccumulation, biotransformation, biomagnification, and effects on ecological species. (Strategic Output ETAM-9)

Methodologically challenging chemicals (MCCs) are chemicals whose physicochemical properties and behaviors are outside the domain ranges of existing predictive tools, methods, and models. Outputs in this category address the biotransformation and bioaccumulation of MCCs in non-mammalian species.

Strategic Output:

- Improve methods and models for predicting the exposure, uptake, accumulation, biotransformation, and impact of methodologically challenging chemicals, including very hydrophobic chemicals as well as chemicals that accumulate in aquatic biota due to specific binding in blood and tissues. (Strategic Output ETAM-10)

Topic 3: Solutions-Driven Translation and Knowledge Delivery

Research in the Solutions-Driven Translation and Knowledge Delivery topic will deliver data and information resources relevant to chemical safety evaluations in a scientifically robust, transparent manner. This work will aid the translation of these approaches by evaluating, establishing, and demonstrating their effectiveness to EPA partners through program-specific applications. The intended impact is for risk assessors and decision makers to have confidence that the new approaches, data, and tools developed in CSS are scientifically sound and improve environmental decision making. The Chemical Safety Analytic (CSA) Research Area will provide highly curated chemical information and develop predictive approaches for chemical safety evaluations. The Informatics, Synthesis, and Integration (ISI) Research Area will develop the online tools and platforms to integrate chemical information to facilitate better access to that information by Agency partners and stakeholders. This topic will make information accessible and usable through web-accessible applications, workflows, and advanced modeling enabled through interoperable systems.

Research Area: Chemical Safety Analytics

Curated data and scientifically defensible, transparent, and publicly accessible models are required for Agency chemical safety decisions, yet many chemicals lack sufficient information on hazard, exposure, dosimetry, or susceptible populations. To address these data gaps, the Chemical Safety Analytics (CSA) Research Area will develop predictive models and tools to establish common principles linking biological and chemical properties to potentials for toxicity, environmental persistence, and transformations in

The CSA Research Area provides predictive tools to estimate hazard and exposure information for data poor chemicals supporting risk-based decisions by Agency partners and stakeholders.

environmental and biological systems. In some cases, other CSS research areas (such as HTT, REMD, and ETAM) will be a source for the predictive models and tools produced by CSA. Case studies will be conducted with partners and stakeholders to evaluate fit-for-purpose applications. The data, tools and models developed by the CSA Research Area will be available through the CompTox Chemicals Dashboard[5] (Williams et al. 2017).

CSS research products include an expanding array of datasets, models, and tools providing chemical, hazard, exposure, pharmacokinetic, and environmental fate information. Efficiently assembling and integrating these data and tools is essential to inform chemical safety decisions. To support Agency partners and stakeholders, CSS strategic outputs support data integration and interpretation in fit-for-purpose applications.

Strategic Output:

- Develop a cheminformatics infrastructure that integrates chemical and biological data, including workflows to interpret and inform bioassay data using molecular structure and physicochemical property values. (Strategic Output CSA-1)

Ecological risk assessments are required to make chemical safety decisions for a variety of species, yet often toxicological data do not exist for species of interest. Approaches to extrapolate existing hazard information across species are needed. To address this need, CSS developed the SeqAPASS tool[6] using biological conservation of protein targets to broadly assess potential species susceptibility differences to chemical exposures. Expanding SeqAPASS tools and associated species extrapolation models is necessary to support Agency partner and stakeholder needs for taxonomic relevance of AOPs and cross-species extrapolation.

Strategic Output:

- Develop data, tools, and models to inform the taxonomic relevance of AOPs and to support cross-species extrapolation for human health and ecological assessments. (Strategic Output CSA-2)

Physical, chemical and biological transformation of chemicals in the environment and endogenous metabolism can contribute to uncertainties in estimating or predicting exposure and dosimetry. This output focuses on tools to estimate transformation and metabolic products to predict the toxicity of metabolites and environmental transformation products, and to reduce uncertainty in chemical prioritization and risk assessment.

Strategic Output:

- Expand modeling capabilities to predict potential metabolites and environmental transformation products for priority chemicals, including emerging contaminants. (Strategic Output CSA-3)

In the absence of sufficient physicochemical or toxicological data, chemical safety assessments rely on predictive approaches to estimate parameters. New QSAR models and read-across methods are needed to predict toxicity values and fill data gaps for ranking and prioritizing chemicals. This output includes

[5] https://comptox.epa.gov/dashboard

[6] https://www.epa.gov/chemical-research/sequence-alignment-predict-across-species-susceptibility

web tools for high-throughput prediction of toxicity and physical properties and features to visualize toxicity data for multiple chemicals and toxicity categories.

Strategic Output:

- Develop new and improve existing structure activity relationship models to predict toxicity for industrial chemicals, pesticides, and emerging contaminants. (Strategic Output CSA-4)

Research Area: Informatics, Synthesis, and Integration

High-throughput NAMs, coupled with continually expanding amounts of traditional toxicological and exposure data, enable more informed chemical safety decisions, assuming data are available and can be integrated. The Informatics, Synthesis, and Integration (ISI) Research Area will develop approaches to present, manage, and utilize the large data streams from CSS research and relevant external data sources. ISI efforts will include partnerships with Agency partners and stakeholders to design systems and approaches to integrate these data into existing assessment workflows and apply these data to chemical safety decisions. The ISI Research Area is the keystone for data dissemination and translation in the CSS.

Products from the ISI Research Area integrate and synthesize chemical information in novel and efficient ways to better inform specific needs of Agency partners and stakeholders. This research area utilizes the mature data outputs from other CSS Research areas.

CSS research has developed data, tools, and products to meet Agency partner and stakeholder needs. These products were developed in multiple research projects, resulting in collections of data and tools across online databases and websites. To increase efficiency in product development and deployment, as well as meet the regulatory needs of our partners, it is necessary to formulate a comprehensive Information Technology (IT) infrastructure. ISI strategic outputs support development of this IT infrastructure and advanced analytical models to address partner and stakeholder needs.

Strategic Outputs:

- Migrate existing dashboard applications along with the relevant data and models into a single architecture. (Strategic Output ISI-1)
- Develop and deliver rapid assessment workflows and applications for chemical evaluation across a range of hazard and/or risk-based decision contexts using data streams and visualizations associated with RapidTox modules. (Strategic Output ISI-2)
- Develop data infrastructure and informatics to support rapid and seamless use of exposure data in decision making, as applications advance beyond prioritization into higher tier assessments. (Strategic Output ISI-3)
- Continue curating and developing mammalian toxicity databases (including new and existing data) to support regulatory decision making, chemical prioritization efforts, predictive model development, and validation of NAM data. (Strategic Output ISI-4)
- Develop risk-based approaches and computational tools to prioritize chemicals for program-specific applications by integrating existing and new data. (Strategic Output ISI-5).

ORD recognizes that partners and stakeholders respond to emerging, unforeseen needs that can benefit from ORD research and technical expertise. In these situations, ORD seeks to balance the relative importance of these emerging needs with the research activities outlined in this StRAP.

Program Design

The structure of the CSS program for FY2019-FY2022 responds to the evolving needs and priorities of partners. The three topics, eight research areas and forty-eight outputs strongly reflect partner needs. The organization of the CSS program also integrates areas of ORD expertise, experience, and capabilities that build on past accomplishments. As such, most of the CSS program components have not changed significantly from the previous StRAP. The organizational and structural changes in the current CSS StRAP include:

- The number of research areas was reduced from 11 to 8.
- The previous research area, *Partner Driven Research* and *Engagement and Outreach*, are eliminated. Given ORD's emphasis and commitment to translational research, which includes being responsive to partners' needs, focusing on solution-oriented research, and engaging partners, the objectives of those former projects are now embedded expectations across the entire CSS program.
- The previous research area, *Life Cycle and Human Exposure Modeling*, is now combined with the former *Rapid Exposure and Dosimetry* research area to form the new research area, *Rapid Exposure Modeling and Dosimetry (REMD)*. This combination is largely driven by convergence of the science and improves the integration of previously segregated efforts.
- The former *Sustainable Chemistry* research area is refined and renamed *Chemical Safety Analytics (CSA)*. This change reflects an emphasis on developing predictive models to provide estimates for various parameters typical of data-poor chemicals and reflects a reduced emphasis on sustainable chemistry.

In summary, the current CSS StRAP structure is revised to better meet the changing needs of CSS partners and stakeholders, while responding to the evolution of chemical safety science. These changes represent a more focused and efficient research program that is attentive to the priority needs of the Agency partners and stakeholders.

Solutions-Driven Research

ORD is committed to producing research results that address real-world problems, inform implementation of environmental regulations and rules, and help EPA partners and stakeholders make timely decisions based on sound science. This commitment includes improving our research processes through application of a solutions-driven research framework that emphasizes:

- Planned partner and stakeholder engagement throughout the research process, starting with problem formulation and informing all elements of research planning, implementation, dissemination, and evaluation;
- A focus on solutions-oriented outputs identified in collaboration with partners and stakeholders;
- Coordination, communication, and collaboration both among ORD researchers and between researchers and partners to develop highly valued integrated research; and,
- Application of research results and outputs in cooperation with partners and stakeholders to develop solutions that are feasible and effective.

Consistent with EPA's Strategic Plan, ORD will work with partners to identify the most important environmental problems they face. Through this engagement, ORD will provide the high-quality science outputs they need to accomplish their human health and environmental protection priorities for chemical safety (USEPA, 2018a). ORD will work with partners and stakeholders to evaluate the

usefulness and effectiveness of the research products in helping them solve their environmental and public health problems.

Adapting to Changing Needs

CSS has worked to understand the needs of the EPA partners and stakeholders and is responding to those needs. However, CSS cannot anticipate all future needs. Unforeseen emerging issues arise that need to be addressed more rapidly. In such cases, CSS will provide the responsive scientific support needed to address emerging issues in a timely manner. This may include redirection of resources and adjustments to ongoing research and product commitments. CSS has the capability to provide scientific leadership and technical expertise for a broad range of emerging chemical safety issues and stands ready to respond accordingly.

Integration Among Research Programs

ORD's six national research programs are coordinated to provide the science that informs Agency and stakeholder decisions and actions. The primary focus of CSS is to support OCSPP in implementing the chemical safety legislation represented in TSCA, FIFRA, and FQPA. Because EPA's programmatic responsibilities for assessing chemical safety are distributed across the Agency, CSS also provides support to other EPA program offices. The CSS research portfolio includes the development of data, tools, and models that are fundamental to the evaluation of chemical safety and are, therefore, relevant across statutes and their associated programs. CSS research efforts with broad applicability include:

- Exposure and dosimetry data and models (REMD);
- Hazard and effects data and models (HTT; ETAM);
- Chemical and species extrapolation models (CSA);
- Cheminformatics resources (ISI); and,
- Predictive tools and analytical workflows (CSA, ISI).

One area of relevance across ORD's National Research Programs is the consideration of sensitive sub-populations, such as children, in public health decision making. Although children, like adults, can be exposed to contaminants in the air, water, soil, dust, food, and consumer products, they may respond differently based on life stage-specific factors that enhance their sensitivity. CSS is developing and applying advanced systems science, reflected in both adverse outcome pathway and virtual tissue modeling activities, which are uniquely positioned to address developmental toxicity in humans. Furthermore, the integration of diverse data and life stage-specific knowledge of exposure, toxicology, and epidemiology will improve our understanding of the role of early life stage chemical exposure on latent health impacts that could occur at any point over the life course.

CSS research activities that complement and support research activities in ORD's other national research programs are outlined below and are illustrative of program integration.

CSS and SSWR Integration

EPA's Office of Water (OW) is responsive to SDWA, CWA, and other legislative mandates, and is primarily supported by ORD's SSWR National Research Program. OW's priorities include chemical safety issues in drinking waters and surface waters, notably the development of criteria values which establish safe concentrations of specific chemicals. Data, tools, and models originating in CSS are routinely used by OW to support criteria development. For example, the ECOTOX Knowledgebase is used in most ambient water quality criteria derivations (CWA, Section 304) conducted by OW and its partners. Thus,

integration and collaboration among CSS and SSWR is critical. Examples of integrative activities among CSS and SSWR include:

- Revision of the 1985 edition of *Guidelines for Deriving Numerical National Water Quality Criteria for the Protection of Aquatic Organisms and Their Uses*;
- Characterization of PFAS chemicals in surface and groundwaters;
- Support for approaches to determine the endocrine disruption activity of chemicals in drinking water;
- Evaluation of chemicals of emerging concern in the environment; and,
- Characterization of microplastics of nanoparticle size.

CSS and SHC Integration

Programs within EPA's Office of Land and Emergency Management (OLEM) implement the Resource Conservation and Recovery Act (RCRA) and the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and are primarily supported by ORD's SHC program. Both RCRA and CERCLA address hazardous waste issues requiring robust, defensible chemical safety information. Both OLEM and OCSPP have interest in the recycling of products and materials and how these materials end up as waste. SHC and CSS are coordinating to better characterize chemical and product life cycles to more effectively inform exposure scenarios. Through SHC, OLEM also has programmatic requirements and activities that rely on the CSS ECOTOX Knowledgebase. Additionally, OLEM has expressed interest in the following topics that are shared by the CSS and SHC research portfolios:

- Characterization of PFAS chemicals and transformation products in the environment and their potential exposure and toxicity;
- Determination of methodologically-challenging chemical behavior; and,
- Development of a data informatics architecture (RapidTox) that supports both TSCA and RCRA activities.

CSS and HHRA Integration

Both CSS and HHRA National Research Programs inform agency activities related to chemical safety. The two research programs work in conjunction to improve chemical risk assessments conducted by the Agency, reduce uncertainties associated with those assessments and increase the speed of delivering chemical information to Agency partners. Interactions between the two programs are helping HHRA become early adopters of the *in vitro* and *in silico* chemical data and the predictive tools being developed by CSS. For example, HHRA is using the EPA CompTox Chemicals Dashboard to inform chemical assessments and incorporate curated data from HHRA systematic review processes. It is anticipated that CSS and HHRA will continue to increase collaborative activities to provide the chemical information and scientifically robust chemical assessments needed by the Agency. For example, the joint development of the RapidTox Dashboard by both CSS and HHRA allows decision makers to access and integrate available chemical-specific information in fit-for-purpose applications such as scoping, screening, prioritization, and/or assessment.

CSS and HSRP Integration

Chemical risk assessors and the emergency response community both require access to reliable chemical information. CSS and HSRP have begun to bring together the information supporting both communities and are exploring the potential application of the EPA CompTox Chemicals Dashboard as a "first-stop-shop" for both communities.

Intramural and Extramural Activities

CSS and Extramural Grants

Extramural research funded through grants and contracts complement and expand the reach of ORD's intramural research program by engaging with external scientists and engineers from academic and non-governmental organizations. Integral to ORD's efforts to address environmental research priorities, extramural research engages the scientific community to strategically respond to current and emerging environmental and public health challenges and help address important scientific knowledge gaps.

CSS uses EPA's Science to Achieve Results (STAR) Grant Program[7] to engage with the academic community through competitive assistance agreements (grants and cooperative agreements). These grants have supported research that have contributed to significant advances in the field of chemical safety, providing cutting-edge science that has enabled new avenues of investigation within CSS. Examples of STAR-funded topics supported by CSS in recent years are provided in Table 2. CSS anticipates continuing to engage with the academic community through STAR to inform and advance the objectives of the CSS program.

Table 2. Examples of STAR Grant topics Supported by CSS

STAR Grant Topics Supported by CSS
Organotypic Culture Models for Predictive Toxicology
Development and Use of Adverse Outcome Pathways that Predict Adverse Developmental Neurotoxicity
Developing High-Throughput Assays for Predictive Modeling of Reproductive and Developmental Toxicity Modulated Through the Endocrine System or Pertinent Pathways in Humans and Species Relevant to Ecological Risk Assessment
Increasing Scientific Data on the Fate, Transport and Behavior of Engineered Nanomaterials in Selected Environmental and Biological Matrices
Systems-Based Research for Evaluating Ecological Impacts of Manufactured Chemicals
New Methods in 21st Century Exposure Science
Susceptibility and Variability in Human Response to Chemical Exposure

Regional Applied Research Effort (RARE)

EPA's Regional Applied Research Effort (RARE)[8] is an Agency program to engage USEPA regions in collaborative research with ORD experts. Topics are proposed by each USEPA region that typically address nearer-term issues of priority to the originating region. ORD resources are used to fund the work. CSS scientists have been active participants in the RARE program and are currently engaged with EPA Region 8 in an FY2018 RARE project, entitled: *Application of 21st century bioanalytical tools to identify sources and effects of bioactive contaminants associated with select municipal wastewater discharges to the South Platte and Colorado River watersheds*.

[7] https://www.epa.gov/research-grants

[8] https://www.epa.gov/sites/production/files/2013-12/documents/rare-201304.pdf

Innovative Proactive Research

Scientific innovation is the engine that enables pioneering research in CSS. Novel means of fostering innovation include open innovation challenges, prizes, and award solicitations, both external to ORD and EPA, and among ORD researchers. Many innovative approaches developed by CSS scientists were initially supported by ORD's Pathfinder Innovation Project (PIP)[9], an internal Agency competition that challenges ORD's scientists to pursue high-risk, high-reward research ideas. Some previous successes include, for example, developing novel bioassay approaches (such as "brain-on-a-chip" models) for developmental neurotoxicity, application of non-targeted analytical methods to measure the "totality of chemical exposure," and innovative approaches to evaluate pollinator health. CSS supports the PIP approach and encourages PIP applications. As appropriate, CSS incorporates the successful innovative developments into its research portfolio.

Interagency and International Collaboration and Outreach

To meet the short- and long-term science needs of Agency partners, CSS actively collaborates with other Federal agencies and engages with the international scientific and chemical regulatory communities. For example, the interagency collaboration for the Tox21 project (Thomas et al. 2018) leverages resources to more efficiently deliver needed chemical information to Agency partners. CSS is actively coordinating research activities with NIEHS to develop toxicological information for perfluorinated chemicals. Additionally, CSS scientists are actively involved in interagency discussions focused on developing and adopting new approach methodologies to toxicity testing.

Internationally, CSS is working with Health Canada and the European Chemicals Agency (ECHA) to improve approaches for sharing chemical information and to develop improved approaches for evaluation of environmental chemicals. Of particular note, is ORD's involvement with the initiative to accelerate the pace of chemical risk assessment (APCRA – Kavlock et al. 2918). These international efforts acknowledge that the regulation and management of chemicals is a global activity. Chemical industries operate globally and have an interest in the regulatory community working together to provide some level of consistency.

Anticipated Research Accomplishments and Projected Impacts

The CSS StRAP FY19-22 emphasizes the application of New Approach Methodologies (NAMs) to solve problems faced by partners and stakeholders. Although the definition of NAMs varies according to the different contexts in which it is used (European Chemicals Agency, 2016; ICCVAM, 2017; USEPA, 2018d), NAMs are broadly defined here as new testing methods (e.g., *in vitro*, *in vivo*, *in silico*, and *in chemico*), analytical tools (e.g., transcriptomics, proteomics, metabolomics), predictive computational toxicology models (e.g., exposure and effects), and informatic and bioinformatic approaches. NAMs serve to accelerate the pace of chemical safety assessments and reduce, refine, and replace vertebrate animal testing. These include high-throughput and high-content methods, tiered testing approaches, AOPs, and use of chemical categories for QSAR and read-across applications.

The use of NAMs has gained broad support and is now mandated, for example, by the Frank R. Lautenberg Chemical Safety Act for the 21st Century. This Act directs EPA to reduce vertebrate animal testing by using NAMs that "provide information of equivalent or better scientific quality and relevance" than conventional approaches. It requires the Agency to "develop a strategic plan to promote the development and implementation of alternative test methods." OCSPP and ORD scientists jointly

[9] https://www.epa.gov/innovation/pathfinder-innovation-projects

collaborated on the development of that strategy, which was released as final in June 2018 (USEPA 2018d) and serves as one of the drivers for the research activities outlined in this StRAP. The development and application of NAMs will play a central role in realizing substantive impacts across several programmatic areas, including informing TSCA implementation, enabling EDSP modernization, and supporting PFAS decisions.

CSS Science Informs TSCA Implementation

In June 2016, Congress passed the Frank R. Lautenberg Chemical Safety for the 21st Century Act. The Lautenberg Act amends TSCA, which is the United States' primary chemical management law. The new law includes much needed improvements to protect American families from the potential health effects of chemicals, including:

- mandatory requirements for EPA to evaluate existing chemicals with clear and enforceable deadlines;
- risk-based chemical assessments with consideration of potentially exposed or susceptible subpopulations (such as infants, children and pregnant women, workers, or the elderly) as well as inclusion of developmental life stages as part of study design;
- increased public transparency for chemical information; and,
- a consistent source of funding for EPA to carry out the responsibilities of the new law.

CSS research is actively supporting OPPT's implementation of the amended TSCA by providing critical chemical data, information, tools, and approaches. Specifically, CSS is assisting with the implementation of the TSCA strategic plan (USEPA 2018d) for developing and adopting new approach methodologies to reduce, refine, and replace the use of vertebrates in toxicity testing and evaluation (TSCA Section 4). CSS scientists are also providing information, tools, and approaches needed to improve and expedite the evaluation of new chemicals (TSCA Section 5). Additionally, CSS activities are supporting the information, data, and approaches for prioritizing existing chemicals (TSCA Section 6).

With the implementation of the activities outlined in this StRAP, it is expected that CSS will provide additional bioassays and other chemical evaluation approaches that will assist with the implementation of the TSCA alternative toxicity testing strategy. New and refined tests for developmental neurotoxicity are planned, as are approaches for screening volatile organic compounds. Additionally, CSS is moving forward with a proof-of-concept study to evaluate the performance of existing human 3D lung culture models to identify chemicals with portal-of-entry effects. Ultimately, the goal of this 3D lung culture work is to develop a non-animal approach to replace the 28-day or 90-day rodent inhalation toxicity study. Working with OPPT to improve and expedite the evaluation of new chemicals will be an ongoing priority. Implementing StRAP activities will also improve approaches currently used by OPPT to evaluate exposures resulting from the use of new chemicals. This has the potential to decrease the time needed by OPPT to evaluate new chemicals.

TSCA, as amended, requires the Agency to complete assessments of a defined number of chemicals determined to be high priority. Initially, OPPT will be turning to the TSCA 2014 Workplan to select high-priority chemicals for assessment. Ultimately, OPPT would like to have an approach and data in place to undertake prioritization evaluations of all chemicals actively produced or used in commerce (currently about 40,000 chemicals). CSS activities are providing data that will inform this prioritization of existing chemicals. For example, CSS scientists are conducting a proof-of-concept study that will inform further development of the long-term chemical prioritization process outlined in an OCSPP document released in September 2018 (USEPA 2018e). That proof-of-concept study is scheduled to be completed in FY2019.

By the end of this StRAP implementation period, it is expected that OPPT will have the data to inform prioritization of the TSCA active inventory list, not just those chemicals in the TSCA workplan.

CSS Science Enables EDSP Modernization

The Food Quality Protection Act (1996) contains provisions calling for the screening and testing of chemicals for endocrine disrupting activity. In response, in 1998 EPA proposed the Endocrine Disrupter Screening Program (EDSP)[10], which was based on the concept of using a two-tiered empirical approach to screening (Tier 1) and testing (Tier 2). The collection of tests for Tier 1 screening includes *in vitro* assays and short term *in vivo* assays as indicators of potential disruption of estrogen, androgen, and thyroid pathways. If a chemical demonstrates potential endocrine disruption activity in Tier 1, then it can be advanced to one or more Tier 2 tests, which are considered definitive dose-response approaches that identify critical-effects concentrations. ORD has a long history of supporting EDSP assay development, assay validation, and interpretation of test data obtained by the Agency. During the twenty years of the program, major advancements have been realized in numerous disciplines, including molecular biology, analytical chemistry, and computational toxicology. In response to these changes, the EDSP has evolved to take advantage of these developments by incorporating NAMs that are more efficient, more informative, and reduce the need for vertebrate animal testing. CSS research and development has been critical to this modernization effort by providing: 1) high-throughput toxicity testing methods and data for estrogen receptor, androgen receptor, thyroid, and steroidogenesis pathways; 2) computational models to predict estrogen receptor and androgen receptor activity; and, 3) adverse outcome pathways to help interpret high-throughput toxicity testing data.

Research activities outlined in the current CSS StRAP will continue to support the evolution of the EDSP through: 1) completion of computational models for estrogen receptor, androgen receptor activity, and steroidogenesis; continued development of high-throughput thyroid assays and associated models; 2) development of species extrapolation approaches; and, 3) development of interactive dashboard tools for data interpretation, translation, and chemical prioritization.

CSS Science Supports PFAS Decision Making

Per- and poly-fluoroalkyl substances, collectively referred to as PFAS, are a large group of several thousand man-made chemicals used in multiple consumer products and industrial applications. Although specific PFAS chemicals, such as PFOA and PFOS, have been studied for over a decade, little information exists for most PFAS chemicals. CSS is helping to expand information about PFAS chemicals by:

- Developing a curated library of PFAS chemicals;
- Expanding the chemical breadth and biological depth of toxicity information for PFAS chemicals;
- Improving exposure characterization of PFAS chemicals in the environment; and,
- Sharing available and emerging PFAS information to EPA partners and stakeholders.

ORD has procured over 400 individual PFAS compounds and developed a curated screening library that is already being used for high-throughput toxicity and pharmacokinetic testing. With the implementation of the activities outlined in this StRAP, the library of PFAS compounds will be expanded and made available to Agency partners, including federal partners (such as NIEHS) and state partners involved in evaluating PFAS compounds. The library is a one-of-a-kind resource that ensures that EPA's testing and evaluations are being performed on identically procured compounds.

[10] https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-edsp-overview

CSS will expand the biological processes and phenotypic responses affected by PFAS exposure using existing tiered toxicity testing approaches and by incorporating newer, high-throughput transcriptomic studies combined with image-based phenotypic profiling. The results of these analyses will expand ORD's ability to perform chemical read-across activities, identify PFAS categories with the greatest potential for adverse health effects, inform prioritization for additional *in vivo* testing, and ultimately inform risk-based decisions for PFAS chemicals.

In addition to expanding the breadth and depth of knowledge concerning the toxicity of PFAS chemicals, CSS activities will also expand understanding of PFAS exposure. Already, CSS non-targeted analyses have been instrumental in identifying PFAS chemicals in the environment and informing Agency enforcement activities (Strynar et al. 2015). Similar, non-targeted analysis approaches will continue under this StRAP and will be used to further characterize the occurrence of PFAS chemicals in environmental media. CSS investments will also expand the capabilities of the Chemical Transformation Stimulator to better predict PFAS degradates that may be detected using non-targeted analysis approaches.

CSS plans to make information about PFAS compounds available in a way that can be understood and used by Agency partners and stakeholders through the Chemistry Dashboard. The CSS Chemistry Dashboard will be the "first-stop shop" for information about PFAS chemicals. When fully developed, it is expected that the CSS RapidTox Dashboard will provide support for conducting rapid risk assessments for chemicals. Ultimately, the information and tools produced by CSS will inform decisions about PFAS chemicals made by Agency partners and stakeholders.

Conclusion

Chemicals are critical to a robust American economy. Thus, efficient, transparent, and scientifically-sound approaches to chemical safety evaluations are essential. To achieve this, CSS is committed to supporting partner and stakeholder needs by providing innovative science designed to solve their priority problems.

CSS seeks to lead the development of new approach methodologies (NAMs) and take advantage of scientific and technological developments that advance efficient evaluations of chemical safety. Through a robust intramural research program, collaborations with partners and stakeholders including academia and other governmental organizations, and through support from an innovative extramural grants program, CSS will build a broader understanding of biology, chemical toxicity, and exposure while providing more rapid, cost-effective approaches that protect human health and valued ecological resources and services.

CSS is committed to translating its work through partner engagement and will maximize the benefits and impacts of our work through outreach and training. This includes continually improving the availability of curated information and executing case studies conducted with partners to demonstrate and improve approaches under real-world circumstances.

CSS will strive to integrate its work within CSS and among other ORD programs to bring added value to the science products that are developed and delivered by the EPA.

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Appendix 1: Partner and stakeholder needs and CSS strategic outputs.

Partner and Stakeholder Needs	Research Area	Strategic Output
Topic 1: Chemical Evaluation		
Research Area: High-Throughput Toxicology (HTT)		
Endocrine Disruptor Screening Program (EDSP): The EDSP has relied on conventional *in vitro* and *in vivo* assays limiting the number of compounds that can be screened in a timely manner. The EDSP21 framework seeks to use New Approach Methodologies (NAMs) and computational approaches to rapidly and more cost-efficiently prioritize and screen chemicals for testing. An additional goal is to reduce and/or replace the use of animals for testing. To reach these goals, assays, models, data, tools, and interpretive frameworks are needed that encompass the modes of action through which estrogen, androgen, and thyroid signaling, and steroid biosynthesis, can be disrupted. (OCSPP; OW; Regions; States)	HTT	HTT-1 - Develop assays, models, data, tools, and interpretive frameworks to support more rapid and cost-effective approaches to screen large inventories of chemicals for their abilities to impact estrogen, androgen, thyroid, and steroidogenesis pathways.
Developmental neurotoxicity (DNT): DNT is an important risk assessment endpoint for chemical assessments. However, currently available *in vivo* methods are costly and do not fully represent important mechanisms and pathways. Therefore, there is a need for alternative approaches for evaluating DNT, including valid *in vitro* methods and modeling approaches. (OCSPP; OLEM)	HTT	HTT-2 - Develop, evaluate, apply, and interpret a developmental neurotoxicity (DNT) battery of assays to reduce uncertainties in chemical safety evaluations.
Methodologically-challenging chemicals (MCCs): MCCs are chemicals whose physicochemical, behavioral, and toxicological properties are not well understood typically fall outside of the range of current assays, models, and analytical methods. There is a need to develop approaches to measure or model the toxicity and exposure of these methodologically-challenging chemicals to inform assessments and decision making. (OCSPP; OLEM; OW; Regions; States)	HTT	HTT-3 - Develop and apply medium- to high-throughput methods to test and deliver novel hazard data on methodologically challenging chemical classes, such as volatile and non-dimethylsulfoxide (DMSO)-soluble chemicals.

Partner and Stakeholder Needs	Research Area	Strategic Output
Tiered testing strategies: Tiered testing strategies are used to evaluate chemical safety in an efficient, risk-based context. These strategies typically use higher throughput approaches to prioritize chemicals for subsequent testing and to screen chemicals for potential hazards. There is a continuing need to develop, demonstrate, and apply emerging technologies to provide actionable information to support tiered decision making. (OCSPP; OLEM, OW, Regions, States)	HTT	HTT-4 - Develop and apply methods and approaches to advance a tiered, high-throughput toxicity testing strategy including high-throughput and high-content methods (e.g., transcriptomics, phenotypic profiling, and other methods) that address key information needs of assessments.
Toxicokinetics: Acceptance and use of *in vitro* data for hazard identification, prediction, and estimation is limited, in part, by uncertainties associated with exposure characterization and metabolism. Most *in vitro* systems lack the biotransformation capabilities of intact *in vivo* systems, raising the possibility of over-estimating the hazard of compounds that may be rapidly metabolized *in vivo* or under-estimating the hazard of compounds that may be transformed to more active metabolites. (OCSPP)	HTT	HTT-5 - Develop methods to incorporate endogenous and exogenous xenobiotic metabolism activity in *in vitro* assay systems.
	HTT	HTT-6 - Evaluating and developing predictive models of the disposition of chemicals in *in vitro* test systems.
Per- and polyfluoroalkyl substances (PFAS): PFAS chemicals are frequently being detected in a variety of environmental media. As a class, PFAS chemicals are structurally diverse and typically lack adequate exposure and hazard information needed to support decisions. (OCSPP; OLEM; OW; Regions; States; Tribes)	HTT	HTT-7 - Develop the PFAS screening library and deliver information from integrated exposure and effects studies.
High throughput toxicity approaches for ecological endpoints: Ecological risk assessments address species across diverse taxonomic groups, many of which have limited or no available data. The clear majority of HTT methods are based on either human or mammalian *in vitro* systems, which results in an under-representation of pathways that are relevant and perhaps unique to non-mammalian taxa. (OCSPP; OW)	HTT	HTT-8 - Develop, evaluate, and apply non-mammalian high-throughput toxicity tests for priority endpoints and pathways in ecological species.

Partner and Stakeholder Needs	Research Area	Strategic Output
Research Area: Rapid Exposure Modeling and Dosimetry (REMD)		
Chemical exposure from consumer products: Exposure models for consumer products require use patterns and exposure factors to develop exposure assessments for consumer pathways and specific consumer users, including potentially exposed and sensitive subpopulations (as defined in TSCA § 3(12) to include infants, children, pregnant women, workers, or the elderly). For many chemicals there are critical gaps in this information. (OCSPP; OCHP; Regions)	REMD	REMD-1: Collect and curate exposure factor-related data (behavior patterns, habits and practices, product composition, chemical fate and transport) for use as inputs to models used in higher tier assessments.
Chemical exposure scenarios and pathways: Chemical exposure evaluations require information to estimate exposure for a variety of high-priority pathways, including scenario-specific data and models particular to consumer products and materials in the indoor environment, as well as occupational, ambient and ecological pathways. (OCSPP; Regions)	REMD	REMD-2: Develop experimental methods, data, and consensus exposure models for various exposure pathways (e.g., consumer, occupational, ambient, indoor environment, and ecological scenarios) that enable high throughput exposure predictions for chemicals.
	REMD	REMD-3: Develop end-of-use models for tracking chemicals in waste streams and the subsequent environmental releases and worker exposures, including novel end-of-life scenarios based on chemical type and function.
	REMD	REMD-4: Expand capabilities of generic scenario processes by minimizing development time and increasing the number of available scenarios. This includes development of models and tools for estimating common scenario needs, data, and methods for estimating new chemical applications, life cycle releases, and occupational exposure support.
Per- and polyfluoroalkyl substances (PFAS): PFAS chemicals are frequently being detected in a variety of environmental media. As a class, PFAS chemicals are structurally diverse and typically lack adequate exposure and hazard information needed to support decisions. (OCSPP; OLEM; OW; Regions; States; Tribes)	REMD	REMD-5: Develop methods, approaches, and frameworks to enable rapid exposure evaluations for PFAS chemicals.

Partner and Stakeholder Needs	Research Area	Strategic Output
Toxicokinetics: Acceptance and use of *in vitro* data for hazard identification, prediction, and estimation is limited, in part, by uncertainties associated with exposure characterization and metabolism. Most *in vitro* systems lack the biotransformation capabilities of intact *in vivo* systems, raising the possibility of over-estimating the hazard of compounds that may be rapidly metabolized *in vivo* or under-estimating the hazard of compounds that may be transformed to more active metabolites. (OCSPP)	REMD	REMD-6: Further development of high-throughput toxicokinetic (HTTK) tools to support *in vitro* to *in vivo* extrapolation. Tools to be developed include those needed to address current sources of uncertainty, challenging chemistries, new exposure routes (e.g., inhalation), and the unique exposures received by sensitive subpopulations.
Chemical exposure modeling: Chemical assessments under TSCA consider exposure and conditions-of-use information which may be reflected in monitoring data. Traditional monitoring, while considered the gold-standard of exposure data, is resource and time intensive. Therefore, methods and tools are necessary to bring next-generation high-throughput monitoring data into agency decision making. (OCSPP)	REMD	REMD-7: Analyze and evaluate new approaches for generating environmental monitoring data, including non-targeted analysis, to identify critical sources and pathways of human and environmental exposures. Develop best practices, workflows, and cross-laboratory evaluations for next-generation monitoring methods.
Chemical information for UVCBs: Over half of the substances on the TSCA inventory are classified as chemical substances of unknown or variable composition (UVCB) with no definite molecular formula. UVCB substances generally cannot be characterized using existing chemical exposure estimation methods. Thus, new methods are needed to further categorize and characterize UVCB exposure. (OCSPP)	REMD	REMD-8: Develop methods to characterize composition of and exposure to chemical substances of unknown or variable composition, complex reaction products, and biological materials.
Research Area: Emerging Materials and Technologies (EMT)		
Engineered nanomaterials (ENMs): Safety assessments of ENMs require information on human and ecological exposure to ENMs from consumer products and environmental releases. Additional data are needed to characterize potential release of and exposure to ENMs. (OCSPP)	EMT	EMT-1: Evaluate environmental release of ENMs and assess and model human and ecological exposures to ENMs, including data for nano-enabled consumer products.
	EMT	EMT-2: Develop a user interface for ORD's existing nanomaterials database, NaKnowBase.

Partner and Stakeholder Needs	Research Area	Strategic Output
Topic 2: Complex Systems Science		
Research Area: Adverse Outcome Pathways (AOP)		
Pathway framework for New Approach Methodologies (NAMs): Successful adoption and use of NAMs and pathway-based data in risk assessments and regulatory decision making depends upon developing confidence that these methods and approaches provide equivalent or better scientific quality and relevance than existing approaches. To achieve this confidence, integrated and synthesized knowledge are needed to establish the scientific rationale that support their use in evaluating the potential human health or ecological consequences that are of management or regulatory concern. (OCSPP: OLEM; OW; Regions; States).	AOP	AOP-1: Develop AOPs for high-priority pathways, design relevant case studies, and disseminate the results through an AOP knowledgebase.
	AOP	AOP-2: Develop and conduct strategic *in vitro* and *in vivo* studies for high-priority AOPs to help establish validity of NAMs approaches, support predictive model development, and reduce vertebrate animal testing through *in vivo* testing refinements for decision-relevant endpoints
	AOP	AOP-3: Conduct research to understand and define biological points of departure, actionable effect levels, and susceptibility factors that need to be considered for application of AOPs.
Pesticide risk assessment: Pesticide risk assessment practices require data submissions that sometimes do not drive the final risk assessment directly. In some cases, the data may not be targeted to toxicological pathways of concern. In others, further analysis and interpretation of the data are required to inform decision-relevant endpoints. (OCSPP)	AOP	AOP-4: Develop rationale and case studies that apply AOPs and HTT data to inform test-order decisions and establish scientific support for waiving testing requirements for pesticides.
Data poor chemicals: Chemical assessments and decisions for data-poor chemicals are often constrained by a lack of ability to generate or solicit additional toxicity data. Consequently, decision makers need to both maximize the information they can extract from available data and utilize predictive approaches and analytical frameworks to evaluate chemicals. (OCSPP; OLEM; OW)	AOP	AOP-5: Provide AOP knowledge to support the use of high-throughput data in expedited chemical assessments for data-poor chemicals.
	AOP	AOP-6: Application of data, models, and tools to support development of revised approach to water quality criteria derivations.

Partner and Stakeholder Needs	Research Area	Strategic Output
Emerging contaminants and mixtures: Emerging contaminants are frequently detected in surface waters and other environmental media, but the toxicological information required to inform decision making is often lacking. Assessments are further complicated because these contaminants typically occur in complex mixtures. Thus, it is difficult to prioritize, monitor, and manage potential risks. (Regions; States; Tribes)	AOP	AOP-7: Conduct site-specific case studies that demonstrate how pathway-based data from existing sources or from effects-based monitoring and surveillance approaches can be used, along with AOPs, to inform risks and associated management actions.
Per- and polyfluoroalkyl substances (PFAS): PFAS chemicals are frequently being detected in a variety of environmental media. As a class, PFAS chemicals are structurally diverse and typically lack adequate exposure and hazard information needed to support decisions. (OCSPP; OLEM; OW; Regions; States; Tribes)	AOP	AOP-8: Develop AOPs relevant to PFAS chemicals and evaluate applicability across species, chemical groupings, and mixtures.
Research Area: Virtual Tissue Modeling (VTM)		
Tiered testing strategies: Tiered testing strategies are used to evaluate chemical safety in an efficient, risk-based context. These strategies typically use higher throughput approaches to prioritize chemicals for subsequent testing and to screen chemicals for potential hazards. There is a continuing need to develop, demonstrate, and apply emerging technologies to provide actionable information to support tiered decision making. (OCSPP; OLEM, OW, Regions, States)	VTM	VTM-1: Develop, characterize, and confirm targeted, mechanistic assays and complex tissue models that bridge between *in vitro* and organismal assays for decision-relevant endpoints.
Vulnerable and sensitive subpopulations: Chemical assessments under TSCA include consideration of risks to vulnerable subpopulations and life stages and to do so with less reliance on traditional animal testing. Thus, new approach methodologies (NAMs) are needed to address potential adverse developmental outcomes that reflect the best available knowledge of human developmental biology. (OCSPP)	VTM	VTM-2: Evaluate the effects of chemical exposure during development on phenotypic responses in human based *in vitro* and virtual tissue model systems to predict chemical hazard.
	VTM	VTM-3: Develop and apply in silico virtual tissue models, agent-based models, and organotypic cell culture models to evaluate and model the effects of chemicals on reproductive and developmental endpoints.

Partner and Stakeholder Needs	Research Area	Strategic Output
Research Area: Ecotoxicological Assessment and Modeling (ETAM)		
Ecological models: Ecological risk assessments are based upon outcomes at the population and community levels. Since it is impractical to test the effects of stressors on populations, decisions must be based on modeled results at the organismal, population, and community levels, including vulnerable life stages and populations. (OCSPP; OLEM)	ETAM	ETAM-1: Translate and incorporate integrated ecological data and models into Agency risk assessment workflows, including information on uptake, bioavailability, dietary assimilation, biotransformation, bioenergetics, behavior, and population effects.
Pesticide risk assessment: Pesticide risk assessment practices require data submissions that sometimes do not drive the final risk assessment directly. In some cases, the data may not be targeted to toxicological pathways of concern. In others, further analysis and interpretation of the data are required to inform decision-relevant endpoints. (OCSPP)	ETAM	ETAM-2: Develop and apply models to translate data from submitted studies into input for models that estimate population- and landscape-level impacts of pesticide use.
Pollinators: Assessing the safety of pesticides to pollinators is an Agency priority. However, methods and data to support evaluation of effects in honey bees and other non-Apis bees are lacking. Furthermore, honey bee colony simulation models are needed to better inform pesticide safety assessments. (OCSPP)	ETAM	ETAM-3: Develop methods and data to assess the impacts of pesticides on honey bee (*Apis mellifera*) and non-*Apis* bees, apply species extrapolation techniques to determine sensitivity differences across species, and further develop and apply honeybee colony simulation models to support pesticide assessments.
ECOTOX Knowledgebase: Virtually all major ecological risk assessments and decisions depend on output from the ECOTOX Knowledgebase. Users of ECOTOX need its content to be current, reflecting the current state of knowledge. Furthermore, new, enhanced analytical capabilities and improved data acquisition and retrieval are needed to better support the varied activities of numerous partners. (OCSPP: OLEM; OW; Regions; States; Tribes)	ETAM	ETAM-4: Improve efficiency, enhance analytical capabilities, and periodically update content of the ECOTOX Knowledgebase, in general and for specific chemicals of interest.
Ecological diversity and species extrapolation: Chemical safety assessments are often conducted with limited or no toxicological data for the animal or plant species of interest. Further, it is frequently impractical to generate new data for those species. Therefore, the sensitivity of species must be estimated based on scientifically-based methods of cross-species extrapolation. The	ETAM	ETAM-5: Advance approaches for using surrogate species in ecological risk assessment, including uncertainty of cross-species extrapolations in minimal data scenarios.
	ETAM	ETAM-6: Develop species-response comparison data with selected high-priority pesticides, linking metabolomics and proteomics with potential molecular initiating events.

Partner and Stakeholder Needs	Research Area	Strategic Output
problem is compounded for ecological assessments by the large number of species in the wild and is particularly problematic for species listed under the Endangered Species Act. (OCSPP; OLEM; Regions)	ETAM	ETAM-7: Assess similarities and differences in mammalian and fish metabolism pathways for selected groups of chemicals and demonstrate use of mammalian metabolism pathway information to predict biotransformation products in fish.
Threatened and endangered species models: The Endangered Species Act outlines requirements to consider potential impacts from the cumulative exposure to multiple environmental chemicals, including pesticides. Models are needed to estimate cumulative exposures and impacts for threatened and endangered species. (OCSPP; OLEM)	ETAM	ETAM-8: Develop improved approaches to protect threatened and endangered species from cumulative exposures to pesticides released to the environment.
Per- and polyfluoroalkyl substances (PFAS): PFAS chemicals are frequently being detected in a variety of environmental media. As a class, PFAS chemicals are structurally diverse and typically lack adequate exposure and hazard information needed to support decisions. (OCSPP; OLEM; OW; Regions; States; Tribes)	ETAM	ETAM-9: Improve understanding of PFAS bioavailability, bioaccumulation, biotransformation, biomagnification, and effects on ecological species.
Methodologically-challenging chemicals (MCCs): MCCs are chemicals whose physicochemical, behavioral, and toxicological properties are not well understood typically fall outside of the range of current assays, models, and analytical methods. There is a need to develop approaches to measure or model the toxicity and exposure of these methodologically-challenging chemicals to inform assessments and decision making. (OCSPP; OLEM; OW; Regions; States)	ETAM	ETAM-10: Improve methods and models for predicting the exposure, uptake, accumulation, biotransformation, and impact of methodologically challenging chemicals, including very hydrophobic chemicals as well as chemicals that accumulate in aquatic biota due to specific binding in blood and tissues.

Partner and Stakeholder Needs	Research Area	Strategic Output
Topic 3: Solutions-Driven Translation and Knowledge Delivery		
Research Area: Chemical Safety Analytics (CSA)		
Chemical curation and informatics: Chemical safety decisions and management can be hindered by the lack of ready-access to the ever-expanding array of data, tools, and models that are relevant to the analyses. Even though many chemical safety resources are available, it may not be clear how the various sources of information might be combined in targeted, efficient workflows to address their specific questions. Furthermore, the use of information from traditionally separate data sources is time-consuming and complex. (OCSPP; OLEM; OW; Regions; States; Tribes)	CSA	CSA-1: Develop a cheminformatics infrastructure integrating chemical and biological data, including workflows to interpret and inform bioassay data using molecular structure and physicochemical property values.
Ecological diversity and species extrapolation: Chemical safety assessments are often conducted with limited or no toxicological data for the animal or plant species of interest. Further, it is frequently impractical to generate new data for those species. Therefore, the sensitivity of species must be estimated based on scientifically-based methods of cross-species extrapolation. The problem is compounded for ecological assessments by the large number of species in the wild and is particularly problematic for species listed under the Endangered Species Act. (OCSPP; OLEM; Regions)	CSA	CSA-2: Develop data, tools, and models to inform the taxonomic relevance of AOPs and to support cross-species extrapolation for human health and ecological assessments.

Partner and Stakeholder Needs	Research Area	Strategic Output
Metabolism and environmental transformation: Regulatory and management decisions for chemicals often consider biotransformation and environmental transformation of the chemical to one or more compounds that may present different hazards than the parent chemical. Thus, tools are needed to identify potential transformation products in biological and environmental systems and to predict the physicochemical properties and toxicity of these products. (OCSPP; OLEM; States)	CSA	CSA-3: Expand modeling capabilities to predict potential metabolites and environmental transformation products for priority chemicals, including emerging contaminants.
ECOTOX Knowledgebase: Virtually all major ecological risk assessments and decisions depend on output from the ECOTOX Knowledgebase. Users of ECOTOX need its content to be current, reflecting the current state of knowledge. Furthermore, new, enhanced analytical capabilities and improved data acquisition and retrieval are needed to better support the varied activities of numerous partners. (OCSPP: OLEM; OW; Regions; States; Tribes)	CSA	CSA-4: Develop new and improve existing structure activity relationship models to predict toxicity for industrial chemicals, pesticides, and emerging contaminants.
Research Area: Informatics, Synthesis, and Integration (ISI)		
Chemical curation and informatics: Chemical safety decisions and management can be hindered by the lack of ready-access to the ever-expanding array of data, tools, and models that are relevant to the analyses. Even though many chemical safety resources are available, it may not be clear how the various sources of information might be combined in targeted, efficient workflows to address their specific questions. Furthermore, the use of information from traditionally separate data sources is time-consuming and complex. (OCSPP; OLEM; OW; Regions; States; Tribes)	ISI	ISI-1: Migrate legacy dashboard applications along with the relevant data and models into a single architecture.

Partner and Stakeholder Needs	Research Area	Strategic Output
	ISI	ISI-2: Develop and deliver rapid assessment workflows and applications for chemical evaluation across a range of hazard and/or risk-based decision-contexts using data streams and visualizations associated with RapidTox modules.
	ISI	ISI-3: Develop data infrastructure and informatics to support rapid and seamless use of exposure data in decision making, as applications advance beyond prioritization into higher tier assessments.
Pathway framework for New Approach Methodologies (NAMs): Successful adoption and use of NAMs and pathway-based data in risk assessments and regulatory decision making depends upon developing confidence that these methods and approaches provide equivalent or better scientific quality and relevance than existing approaches. To achieve this confidence, integrated and synthesized knowledge are needed to establish the scientific rationale that support their use in evaluating the potential human health or ecological consequences that are of management or regulatory concern. (OCSPP: OLEM; OW; Regions; States)	ISI	ISI-4: Continued curation and development of mammalian toxicity databases (including new and legacy data) to support regulatory decision making, chemical prioritization efforts, predictive model development, and validation of NAM data.

Partner and Stakeholder Needs	Research Area	Strategic Output
Chemical prioritization: Several lists or inventories of chemicals that may warrant assessment exist, originating in various Agency programs. The chemicals on these lists typically have limited data to inform decisions and may require additional studies. Thus, it is important to prioritize chemicals to focus resources and attention on those chemicals with the highest concern. The performance of established prioritization approaches needs to be assessed and more efficient approaches need to be developed to take advantage of recently developed predictive tools and models. (OCSPP; OLEM; OW; Regions; Tribes; States)	ISI	ISI-5: Develop risk-based approaches and computational tools to prioritize chemicals for program-specific applications, integrating existing and new data on, for example, chemical properties, hazard, exposure, persistence, and bioaccumulation.

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Appendix 2: Partner and stakeholder engagements to inform CSS StRAP development.

Meeting Title/Outreach Effort	Frequency/Date	Meeting Purpose
Individual Events		
Stakeholder Engagement Workshop	August 29-30, 2017	The Stakeholder Engagement Workshop was held to discuss how to better connect ORD staff working on various stakeholder outreach activities, develop a more strategic approach to ORD stakeholder outreach to maximize the impact of our efforts to be more efficient with staff time and resources, and to better translate and package research for stakeholders and partners.
Joint ORD-OPPT Exposure from Consumer Products Workshop	September 13, 2017	ORD exposure scientists met with OPPT to discuss approaches to evaluate potential chemical exposure from consumer products. The objective of this workshop was to exchange information on existing tools and discuss future exposure science related needs. The workshop helped to identify opportunities for additional collaboration between ORD and OPPT for the successful implementation of TSCA and informed development of specific research activities.
Joint ORD-OPPT Occupational Exposure Workshop	October 12, 2017	Joint ORD-OPPT workshop focused on chemical exposure from consumer products.
CSS-OPPT Discussion of Improving Exposure Information for TSCA Chemical Prioritization and Evaluation	October 20, 2017	As part of ongoing discussions to improve the set of exposure information and tools available to support TSCA activities, CSS and OPPT scientists met to discuss joint activities focused on chemical exposure from consumer products and occupational exposure to chemicals.
Joint ORD-OPPT Ambient Exposure Workshop	October 31, 2017	This workshop continued ORD-OPPT discussions on improving estimates of chemical exposure estimates used for the evaluation of new and existing chemicals under TSCA. The workshops strengthened and expanded working relationships between ORD and OPPT and expanded the breadth of science that can be used for the implementation of TSCA.
Translational Science Workshop	November 29-30, 2017	The Translational Science Workshop purpose was to introduce ORD scientists and managers to the Translational Science for Environment and Public Health framework and provide training and guidance for implementing the framework in designing, implementing, and applying ORD research.

Meeting Title/Outreach Effort	Frequency/Date	Meeting Purpose
FIFRA Scientific Advisory Panel	November 28-30, 2017	The Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (FIFRA SAP) met on November 28-30 to discuss the topic of "Continuing Development of Alternative High-Throughput Screens to Determine Endocrine Disruption, focusing on Androgen Receptor, Steroidogenesis, and Thyroid Pathways." The SAP provided comment on a paper prepared by OCSPP and ORD scientists. Input from the SAP helped inform the development of directions for research activities involving endocrine testing and screening approaches.
Adverse Outcome Pathways Workshop	January 17-18, 2018	CSS hosted a workshop involving program (OPPT, OPP, OSCP, OLEM, OW) and regional office partners to discuss the development and use of adverse outcome pathways (AOPs). The CSS team collected input on how research partners use AOPs in the implementation of their programs, what pathways are of most interest and need further development, and what are the barriers to the use of AOPs.
Federal Information Exchange on PFAS	February 5-6, 2018	The Federal Information Exchange on PFAS meeting was sponsored by the Toxics & Risks Subcommittee of the NSTC Committee on Environment, Natural Resources, and Sustainability, co-chaired by the DoD, EPA, and NIH. This workshop established a foundation of common knowledge across federal agencies, and facilitated future information-sharing across federal agencies, from high-level officials to laboratory researchers.
CSS-HHRA/ECOS Cross-Media Team Meeting	May 3, 2018	As part of ongoing activities to identify specific research needs from states, CSS and HHRA met with the Environmental Council of States (ECOS) Cross-Media Team.
3rd Annual STAR Organotypic Culture Models (OCM) for Predictive Toxicology Research Centers Progress Review	May 22-23, 2018	The CSS funded STAR OCM Centers develop cell-based organoids and microscale tissue systems that collect data on reactions to chemical exposure under normal physiological conditions. Progress coming from the third year of the OCM Centers, their EPA collaborators, and other colleagues were presented and discussed at this meeting.
ORD/OCSPP Discussion of CSS StRAP Development	May 30, 2018	OCSPP senior management provided comments on the initial outline of the topics and research areas to be included in the CSS StRAP.

Meeting Title/Outreach Effort	Frequency/Date	Meeting Purpose
National Academy of Science Meeting	June 7, 2018	CSS staff met with representatives from the National Academy of Science. The purpose of the meeting was to trade information concerning future directions for our programs and outline potential research areas of mutual interest.
National Tribal Toxics Council Meeting	July 17, 2018	CSS and HHRA provided an update on StRAP development for the monthly meeting of the National Tribal Toxics Council. Presentations focused on the structure of the revised StRAPs for the CSS and HHRA National Programs and specific research activities that may be of interest to tribal communities.
Tribal Pesticide Program Council Meeting	July 18, 2018	CSS provided an update on CSS StRAP development for the monthly meeting of the Tribal Pesticide Program Council. The presentation focused on the structure of the revised StRAP, highlighted specific research activities that may be of interest to tribal communities, and provided details for ongoing research activities for ecological risk assessment.
National Tribal Science Council Meeting	July 31-August 1, 2018	ORD National Program Directors provided an overview of StRAP development for the National Tribal Science Council Meeting. NPDs highlighted specific research activities relevant to tribal communities and to help address environmental concerns.
ORD/OCSPP Strategic Research Plan discussion	October 18, 2018	OCSPP senior management provided feedback on the research areas, need statements and strategic outputs presented in an earlier version of the CSS StRAP. OCSPP ranked 84% of the stated outputs as high or medium priority.
Ongoing Interactions		
Developmental Neurotoxicity (DNT) Work Group	Ongoing/Periodic Interactions	A DNT Workgroup was formed to bring together researchers from ORD and Program Office Partners to discuss research needs and approaches for the development of alternative methods for Developmental Neurotoxicity Testing done in the ORD under the auspices of the CSS National Research Program.

Meeting Title/Outreach Effort	Frequency/Date	Meeting Purpose
EDSP Workgroup	Ongoing Bi-Monthly Interactions	The Endocrine Disruptor Screening Program (EDSP) uses a two-tiered approach to screen pesticides, chemicals, and environmental contaminants for their potential effect on estrogen, androgen and thyroid hormone systems. Participants in the EDSP Workgroup provide expertise, answer questions, draft language, and review important documents to further the program.
Alternative Testing Strategies Meetings	Ongoing Tri-monthly Interactions	Regular meetings July 2017 through June 2018 with ORD and OCSPP to develop and complete the TSACA Alternative Testing strategy document (USEPA 2018e). Quarterly meetings of OCSPP and ORD staff to guide the implementation of the strategy document.
Children's Environmental Health Partner Alliance Coordination Team (CEH PACT)	Ongoing Monthly Interactions	The Children's Environmental Health (CEH) Research PACT (Partner Alliance Coordination Team) was formed to facilitate cross-ORD implementation of the CEH Research Roadmap, enhance communication about CEH research among EPA researchers, partners and stakeholders, and serve as a resource to EPA leadership on CEH-related research. The PACT provides materials to Agency partners as needed, develops CEH research web content, develops CEH relevant RFAs, provides input on CEH webinar series; workshops, or conferences supported by ORD.
Monthly Implementation Meeting	Ongoing Monthly Interactions	CSS Implementation Team Meetings are held once a month to continue open dialogue between CSS and EPA Program Offices and Regions. The first part of the meeting is dedicated to updates from Program Offices, Regions and CSS. The meetings conclude with a short webinar from a CSS scientist highlighting a research topic of interest.
Accelerating the Pace of Chemical Risk Assessment Meetings (APCRA)	Ongoing/Periodic Interactions	These meetings include ORD/PO and representatives from international chemical safety management regulatory bodies and are focused on case studies leading to transformational changes in chemical risk assessment.
AOPDD Webinar	Ongoing Monthly Interactions	The purpose of this Adverse Outcome Pathway (AOP) webinar series is to strengthen CSS AOP research efforts by facilitating communication and collaboration between CSS, Program Offices, and Regions.

Meeting Title/Outreach Effort	Frequency/Date	Meeting Purpose
CSS Science Webinars	Ongoing Monthly Interactions	The CSS monthly Science Webinars inform internal Agency partners and collaborators of current and on-going CSS science and enhance communication and collaboration between CSS, Program Offices, and Regions.
Biotechnology Community of Practice	Ongoing/Periodic Interactions	The Biotechnology Community of Practice is an agency-wide group of scientists exchanging information about the application of biotechnology and the development of synthetic biology with potential application to environmental problems.
Pollinators Community of Practice	Ongoing/Periodic Interactions	The Pollinators Community of Practice was formed to maintain communications among ORD, Regional, and Program Offices on issues related to pollinator protection, ensure that ORD's efforts in pollinator research align with Program Office needs.
Program Office Meetings	Ongoing/Periodic Interactions	The CSS National Program Director and Deputy National Program Director routinely meet with Agency Program Office Senior Management to discuss progress on ongoing research activities, deliver completed products, and identify additional research needs. These meetings occur biweekly, monthly and quarterly, depending upon the program office.

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Appendix 3: State needs as conveyed to EPA by the Environmental Council of the States (ECOS)

Source	Identified State Need	CSS Research Area of Relevance
Water		
2016 Survey	Water Quality/Surface Water Quality/GW Quality	New approaches to collecting and analyzing monitoring data (e.g., non-targeted and suspect screening)
	More work on wastewater treatment plants and landfills (Michigan)	Effects-based monitoring and surveillance in conjunction with adverse outcome pathways (AOPs) to understand risks and management decision associated with wastewater plant discharges.
Emerging Contaminants		
2016 Survey	Manage new chemicals of emerging concern and existing chemicals	Assays, models, tools, data and interpretive frameworks to screen and prioritize chemicals for exposure, toxicity, endocrine disruption, and risk; web-based infrastructure (i.e., dashboards)
	Improve and understand process	Improved access to integrated chemical safety information on exposure, toxicity, and persistence including information on methodologically challenging compounds
	Adapt and respond to emergencies	Methods, approaches and frameworks for rapid response to emerging high-profile chemicals such as PFAS in water and PCBs in consumer products; Rapid Assessment workflows and applications for hazard and/or risk-based decision contexts
	More info for PFAS, surface water standards, fish consumption and biosolids advisory levels	PFAS screening library for testing, method development and analyte confirmation; improved understanding of PFAS uptake and bioavailability in ecological species
Cross-Media		
2017-2018 Media meeting	Help with/alternatives to choosing emerging contaminant surrogates for regulation (Oklahoma)	Fundamental data, knowledge infrastructure, and complex systems understanding for rapid chemical evaluation and to predict potential impacts
	Nanomaterial measurement (Washington)	Develop, collate, mine, and apply information on engineered nanomaterials to support risk-based decisions
	PFAS • Remediation techniques to accompany EPA's work on analysis/detection (Oklahoma) • Health and environmental impacts of PFAS (Tennessee)	Developing a curated library of PFAS chemicals; expanding the chemical breadth and biological depth of toxicity information for PFAS chemicals; developing tool to predict transformation products of PFAS in the environment and improve exposure characterization of PFAS chemicals